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IN THE DRAWINGS

Applicant encloses revised drawings to overcome the objections set out in the Notice of the Draft Persons Patent Drawing Review. The revised drawings (Figures 1-8) are enclosed to overcome the objections under paragraphs 5, 10 and 12. In view thereof, Applicant respectfully submits that the drawings are now in order.

IN THE CLAIMS

The Examiner has objected to the claims on the basis of 35 U.S.C. §112 and under 37 C.F.R. 1.75 (c) as being in improper form. The claims have been revised to overcome the objections of the Examiner. Therefore in the claims please make the following amendments:

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1. (amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours.

2. (amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours.

4. (amended) The preparation of claim 1[,] or 2 [or 3] wherein the Diltiazem is in the form of Diltiazem HCl.

5. (amended) The preparation of claim 1[,] or 2[, 3 or 4] wherein the preparation is a diffusion controlled preparation.

6. (amended) The preparation of claim 1[,] or 2[, 3, 4 or 5] wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

7. (amended) The preparation of claim 1[,] or 2[, 3, 4, 5 or 6] in capsule form.

8. (amended) The preparation of claim 1[,] or 2[, 3, 4, 5 or 6] in tablet form.

9. (amended) The preparation of claim 1[,] or 2[, 3, 4, 5, 6, 7 or 8] wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises [comprising] a central core of [containing] the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane [and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent].

11. (amended) The preparation of claim 10 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each microgranule [bead], ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

12. (amended) The preparation of claim 9, 10 or 11 wherein the membrane comprises a water-dispersible or water-soluble polymer [(such as HPMC)] and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as

Eudragit NE30D (a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester)] which hydrates the preparation.

13. (amended) The preparation of claim 9 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer [(such as HPMC)] and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester)] which hydrates the preparation.

14. (amended) The preparation of claim 9, 10, 11, 12 or 13 wherein the membrane comprises a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30D] and hydroxypropylmethylcellulose.

15. (amended) The preparation of claim 14 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule [bead], and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

16. (amended) The preparation of claim 10 or 11 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propenyl)oxy]-chloride ethanaminium polymer with ethyl-2-propenoate and methyl-2-methyl-2-propenoate [Eudragit RS, Eudragit RL] and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

18. (amended) The preparation of claim 17 wherein the dissolution agent is an organic acid selected from the group consisting of [such as] adipic acid, ascorbic

acid, citric acid, fumaric acid, malic acid, succinic acid, and tartaric acid, [and the like] which permits the diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into [the] higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

44. (amended) The preparation of claim 9, 10, 11, 12, 13, 14, 15 or 16 wherein the wetting agent is selected from the group consisting of:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose, [commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.) such as sucrose stearate marketed under the trade name of Crodesta];
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene [(Brijs, Renex and Eumulgines, Henkel, RFA)];
sorbitan fatty acid esters [(Span, Atlas, U.S.A.)];
polyglycides-glycerides and polyglycides-alcohols esters [(Gelucires, Gattefosse, France)] and
Metal salts [such as NaCl or sodium lauryl sulphate].

45. (amended) The preparation of claim 9 wherein the wetting agent is in association with the diltiazem in the microgranule [bead] and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer [such as hydroxypropylmethylcellulose] and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [such as Eudragit NE30D] enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

48. (amended) The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45 in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose [(Avicel ph101)]	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate [(crodesta F150)]	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30 D] (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

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50. (amended) The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45 in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

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(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer [such as hydroxypropylmethylcellulose]; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

52. (amended) The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45 in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer [such as hydroxypropylmethylcellulose]; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid

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methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

56. (amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

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(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer [such as hydroxypropylmethylcellulose]; and

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(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

59. (amended) The preparation of claim 56, 57 or 58 wherein the core and membrane comprise:

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(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

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(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer [such as hydroxypropylmethylcellulose]; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

60. (amended) The preparation of claim 56, 57 or 58 wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30 D] (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

REMARKS

Claims 1-62, as amended, remain in the Application.

Claim Objections - Election/Restriction

The Examiner has required that Applicant elect a single disclosed species under 35 U.S.C. §121. Applicant elects the following species: capsules.

The said elected species reads on the following claims: Claims 1-7, 9-25, 27-53, 56-60 and 62.

Multiple Dependencies

The Examiner has objected to Claims 4-18, 22-55, 61 and 62 under 37 CFR 1.75(c) as being improper. Applicant has amended the claims in order to